

ANALGETIC DOSAGE FORMS THAT ARE RESISTANT TO PARENTERAL
AND INHALATION DOSING AND HAVE REDUCED SIDE EFFECTS

10 FIELD OF INVENTION

The invention provides a means for reducing the potential for the abuse of potent opiate oral analgetic drugs by preventing the recovery of the opiate oral analgetic in
15 a form that allows the preparation of a parenteral or inhalable dosage formulation.

This invention relates to solid dosage forms of oral analgetic drugs which are effective for pain control (or treating diarrhea) and are not adapted for recovery of
20 the opiate analgetic. The invention also provides a novel process for preparing the novel formulations of the invention and reducing the side effects of analgetic preparations.

25 BACKGROUND OF THE INVENTION

The term opiate applies to a legal classification of drugs that include those which are derived from Papaver somniferum and other drugs that have been listed by
30 authorities as having the same or similar addictive potential or properties that were the basis for the regulation or prohibition of the use of derivatives of Papaver somniferum. Morphine and codeine are well known opiates that have previously been widely abused and in
35 recent years the use of other derivatives of Papaver somniferum such as oxycodone have been widely abused because it is not difficult to prepare an injectable form of oxycodone by merely dissolving the oral oxycontin tablets in water and thus preparing an injectable form of
40 the oxycodone. U.S. 3,773,955 describes the making of a composition of oxycodone and naloxone to prevent the abuse of oxycodone by taking advantage of the known opiate blocking effect of naloxone. Combinations of

5 pentazocine and naloxone and burenorphine and naloxone
have also been described. However, these formulations,
which contain naloxone, have been relatively easy to
separate using high performance liquid chromatography
(HPLC) or other techniques.

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In the prior art, paregoric (camphorated tincture of
opium) was sold to the general public as a remedy for
diarrhea or for teething pain because it contained a
small amount of opium. The sale of this preparation
15 without a prescription was discontinued because addicted
individuals would separate the camphor by cooling and/or
filtering the preparation, boiling off the alcohol and
then re-dissolving the opium containing residue in water
to make an injectable preparation. This resulted in the
20 loss to the general public of an effective diarrhea
remedy which is more effective and faster acting than the
insoluble drugs Lomotil and Imodium which are widely
used. Furthermore, Lomotil and Imodium are toxic to
children thus the FDA bans the use of these drugs in this
25 patient population.

Methadone is an opiate analgetic that has been
available in tablet and liquid formulations for more than
50 years. This drug is an important drug in the treatment
of opiate addiction in many dependent individuals.
30 Typically, methadone is either administered at a clinic
to an addicted patient as an oral liquid in the presence
of a health professional to reduce the potential for
diversion of the drug for street abuse by addicted
persons who are not under treatment and typically use
35 methadone in combination with other drugs. A supply of
the liquid methadone is usually provided for self-
administration by the patient use between clinic visits
typically in the form of a Kool_Aid or other liquid
flavored solution. These solutions require refrigeration
40 and accidental poisonings of children and other non-
addicted individuals has been known to occur.

5 It is apparent that a need exists for oral dosage forms
of opiate anaesthetics that are stable, contain an opiate
antagonist, and are resistant to conventional separation
techniques that are designed to permit recovery of the
opiate in a form that is pure enough to prepare a
10 parenteral dose of the drug for illicit use.

SUMMARY OF THE INVENTION

The present invention is based on the discovery that an
15 opiate and an opiate antagonist may be combined in an
oral dosage form with a hydrocolloid containing excipient
that comprises a gel forming agent which swells in the
presence of water and forms a gel type matrix that
substantially prevents the selective extraction of the
20 opiate from the opiate-opiate antagonist mixture or the
use of the highly viscous hydrocolloid solution as a
injectable preparation and provide a formulation having
reduced side effects. The invention also includes solid
oral dosage formulations of an opiate and a hydrocolloid
25 excipient that comprises a gel forming agent which swells
in the presence of water and forms a gel type matrix that
substantially prevents the making of a parenteral
injection of the opiate through the formation of the
highly viscous matrix that can not be passed through a
30 hypodermic needle.

Accordingly, it is a primary object of the present
invention to provide a novel stable, oral dosage form of
a combination of an orally effective opiate drug that
35 cannot be made into a parenteral formulation of the
opiate drug.

It is also an object of this invention to provide a novel
oral tablet of an opiate drug in combination with an
40 opiate antagonist which is resistant to the use of
conventional separation techniques that are applied to
separate an opiate drug from an opiate antagonist.

5 It is also an object of this invention to provide a solid dosage form of an opiate drug that forms a non-injectable, highly viscous gel when the solid dosage form is placed in water.

10 It is also an object of the invention to provide a method of formulating a solid oral dosage from an opiate and an opiate antagonist which is resistant to conventional separation techniques that may be applied to separate the opiate from the opiate antagonist by adding
15 a hydrocolloid forming material to the solid dosage formulation.

These and other objects of the invention will become apparent from a review of the appended specification.

20

DETAILED DESCRIPTION OF THE INVENTION

The above objects are realized by a solid oral dosage form, which comprises an opiate and an opiate antagonist
25 and an excipient which comprises a hydrocolloid. The preferred form of the solid dosage form is a tablet but it is also possible to formulate the solid dosage form of the invention in hard or soft gelatin capsules. Without being bound by any theory under which the invention
30 operates, it is believed that the addition of a hydrocolloid causes the solid dosage form to swell in the presence of water and form a highly viscous matrix or slurry that is impossible to pass through a hypodermic needle or pass through any known type of filtration
35 means. The matrix that is formed also causes the soluble opiate and opiate antagonist to become trapped in the expanding matrix that the hydrocolloid forms as it is exposed to water and makes it difficult to use conventional separation techniques to obtain concentrated
40 form of the opiate drug apart from the opiate antagonist and the hydrocolloid material.

5 The principal side effect that is avoided by the
invention is constipation. This is achieved by the action
of the separate opiate antagonist in enteric form and it
is believed that the hydrocolloid also exerts a positive
beneficial effect. The opiates that may be used in the
10 invention include all known opiates including but not
limited to morphine, codeine, dilaudid, pantopon,
methadone, paregoric, pentazocine, buprenorphine,
fentanyl, oxycodone, oxymorphone, hydromorphone,
hydrocodone, propoxyphene , nalbuphine, meperidine and
15 the like.

The solid pharmaceutical dosage forms of the invention
may also include an amount of enteric coated opiate
antagonist pellets which are effective to prevent opiate
20 induced constipation. The amount, per unit dose of
opiate, of the enteric coated opiate antagonist pellets
may vary from 3 to 10mg per unit dose. The enteric
coating agents include Eudragit S100, hydroxypropyl
methylcellulose, polyvinylpyrrolidone, and the like. It
25 is understood that where polymeric materials are used,
the molecular weight will be selected to provide the
desired effect.

30 The opiate antagonists include but are not limited to
naloxone, naltrexone, methylnaltrexone, or naloxonazine.
The preferred opiate antagonist is naloxone which has a
very high oral/parenteral ratio, is completely devoid of
35 agonist activity and is ideally suited for use as a
denaturant for solid dosage forms of opiates.

The hydrocolloids that form a gel like matrix when
contacted with water are well known and are described in
40 the literature. These materials are generally defined as
materials that include increase viscosity, and contribute
to the thickening and/or gelation when contacted with
water. The hydrocolloids include cellulose derivatives

5 such as high viscosity hydroxypropyl methyl cellulose
having a viscosity of above 3000 mPa s (2% aq. soln. @
20°C), agar, alginates, zein from Zea mays (Zein F-
4000) such as carrageenan, guar gum, locust bean gum,
xanthan gum and the like.

10 As indicated above the dosage forms of the present
invention may comprise auxiliary excipients such as for
example diluents, binders, lubricants, surfactants,
disintegrants, plasticisers, anti-tack agents, opacifying
agents, pigments, and the like. As will be appreciated by
15 those skilled in the art, the exact choice of excipient
and their relative amounts will depend to some extent on
the final oral dosage form.

Suitable diluents include for example pharmaceutically
20 acceptable inert fillers such as microcrystalline
cellulose, lactose, starch, dibasic calcium phosphate,
saccharides, and/or mixtures of the foregoing. Examples
of microcrystalline celluloses include (Avicel PH 200,
Avicel PH 102, Avicel PH 112, Avicel PH 101, Avicel PH
25 3020; examples of lactose include lactose monohydrate,
lactose; in addition, mannitol; sucrose; and dextrose may
be used.

Suitable binders include for example starch, povidone,
30 low viscosity hydroxypropylmethylcellulose such as
Methocel E-5 Prem. LV, pregelatinised starch,
hydroxypropylcellulose and/or mixtures of the foregoing.
Suitable lubricants, including agents that act on the
flowability of the powder to be compressed are, for
35 example, stearic acid, talc, colloidal silicon dioxide,
calcium or magnesium stearate, or sodium stearyl
fumarate,

Suitable disintegrants include for example crosslinked
40 polyvinyl pyrrolidone, various starches such as potato
starch, corn starch, potato starch, rice starch and
modified starches, croscopovidone, sodium starch glycolate
croscarmellose sodium, and the like or mixtures thereof.

5 As indicated above the dosage forms of the present
invention may comprise auxiliary, excipients such as for
example lubricants, plasticisers, anti-tack agents,
opacifying agents,) pigments, and such like, As will be
appreciated by those skilled in the art, the exact choice
10 of excipient and their relative amounts will depend to
some extent on the final oral dosage form.

Suitable lubricants, including agents that act on the
flowability of the powder to be compressed are, for
15 example, colloidal silicon dioxide such as Aerosil 200
(Aerosil is a Trade Mark); talc; stearic acid, magnesium
stearate, calcium stearate and sodium stearyl fumarate.

Granulations for preparing tablets according to the
20 invention can be manufactured in accordance with standard
procedures in which the opiate drug, the opiate
antagonist and the hydrogel forming material may be
combined with suitable excipients prior to mixing and
forming compressible granules by adding solution of a
25 binder in a low or high shear mixer or by fluidized bed
granulation. The granulate is dried, preferably in a
fluidized bed dryer. The dried granulate is sieved and
mixed with lubricants and disintegrants. Alternatively
the manufacture of granules can be achieved by direct
30 mixing of the directly compressible excipients or by
roller compaction.

The dosage forms of the invention will comprise a
therapeutically effective amount of the opiate analgetic,
35 an amount of the opiate antagonist which is effective to
antagonize the additive potential of the opiate analgetic
drug and an amount of the hydrocolloid which will cause
the dosage form to be converted into a non-injectable gel
like mass when the dosage form is placed in from 30 to
40 100ml of an aqueous fluid such as water.

EXAMPLE 1

(Oxycodone-naloxone) (5 + 0.25) For analgesia

Components

10	Oxycodone hydrochloride	500 gm
	Naloxone hydrochloride	40 gm
	Starch U.S.P. (for paste)	1000 gm
	Starch U.S.P. (for granulation)	40000 gm
	Keltrol F (xanthan gum from Xanthamonas campetris)	
15	950 gm (C.P. Kelco U.S., Wilmington, DE 19894)	
	Locust bean gum from Seratonia siliqua	3700 gm
	(Degussa Texturant	
	Systems U.S. Atlanta, GA 30340)	
	Monobasic calcium phosphate	700 gm
20	Dibasic calcium phosphate	700 gm
	Microcrystalline cellulose (Avicel)	24800 gm (FMC
	Biopolymers, Newark, DE)	
	Kelcoloid HVF 18 (30 mesh propylene	
	glycol alginate	10000 gm (ISP
25	Alginates, San	
	Diego CA 92113)	
	F .D. and C. yellow lake no. 5	500 gm
	Zein F-300 20-30 mesh from Zea mays	5000 gm
	(Freeman Industries	
30	LLC, Tuckahoe, NY 10701	
	Magnesium stearate U.S.P.	950 gm
	Total	91225 gm

35 A starch paste is prepared by mixing 1000 gm of starch with 8000 gm of deionized water. A separate blend is prepared by mixing 2500 gm of starch, 2000 gm of oxycodone hydrochloride and 400025 gm of anhydrous lactose. Naloxone hydrochloride (200 gm) is dissolved in 1500 gm of deionized water. The starch paste and the

40 solution of naloxone hydrochloride are wet granulated with the dry blend of starch, methadone hydrochloride and anhydrous lactose. The wet granulation is passed through a No.10 mesh screen, spread on trays and dried

- 5 for 18 hours at 120° F. The moisture content of the dried granulation is between 2.0-3.5%. The dried granulation is then consecutively passed through a No. 12 mesh screen and a No. 30 mesh screen.
- 10 To the dried granulation there are added 950 gm of xanthan gum (Keltrol F) (from *Xanthomonas campestris*), 3700 gm of locust bean gum (from *Seratonia siliqua*), 100 gm of monobasic calcium phosphate, 100 gm of dibasic calcium phosphate, 24800 gm of microcrystalline cellulose
- 15 (Avicel), and 500 gm of F D & C yellow lake No.5 and the mixture is blended for 15 minutes. Propylene glycol alginate (Kelcoloid HVF) which has been compacted and granulated to produce 18-30 mesh granules 10000 gm), Zein (F- 4000) (from *Zea mays*) which has been compacted and
- 20 granulated to produce 20-30 mesh granules (5000 gm), and 950 gm of magnesium stearate are added and the mixture is blended for 5 minutes. The mixture is then admixed with 10000 gm of enteric coated micro spheres containing 1000 gm of naloxone hydrochloride. This mixture makes 100,000
- 25 tablets each weighing 262 gm and containing 5 mg of oxycodone hydrochloride and 0.5 mg of naloxone hydrochloride. A tablet disintegrates in the U.S.P. disintegration test in less than 5 minutes. A tablet crushed and dispersed in 20 cc of water at 25° C. gives a
- 30 thick gel which cannot be filtered through either cotton or coarse filter paper to obtain any filtrate, and cannot be drawn or discharged through an 18 gauge hypodermic needle.

Inasmuch as diversion of analgesics to parenteral abuse

35 may be a theoretical possibility, in spite of the above safeguards, this diversion can be tracked by adding 10% by weight of a microtaggant such as Microtaggant™, a, which is available from (Microtrace LLC, Minneapolis, MN 55449-7216).

- 40 Optionally one may add 10000 gm of enteric coated microspheres containing 500 gm of naloxone hydrochloride

- 5 prepared according to the procedure of Example 5 to prevent constipation as a side effect. The above mixture may be tabletted or filled into hard gelatin capsules .

EXAMPLE 2

(Methadone-Naloxone) (40 + 2gm)

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A methadone-naloxone gum tablet was produced using the procedure described below:

List of ingredients

15

16000 gm methadone hydrochloride U.S.P.

800gm naloxone hydrochloride

4000 gm starch U.S.P. (for paste)

20

10000 gm starch U.S. P. (for granulation)

160100 gm lactose U.S.P, anhydrous

25

3700 gm keltrol F (xanthan gum from *Xanthamonas campestris*)

14800 gm locust bean gum (from *Seratonia siliqua*)

30

2800 gm monobasic calcium phosphate, anhydrous

2800 gm dibasic calcium phosphate N.F., anhydrous

99200 gm microcrystalline cellulose

35

40000 gm Kelcoloid HVF 18-30 mesh (propylene glycol alginate)

2000 gm F D & C Yellow No. 5 lake

40

20000gm Zein F-4000, 20-30 mesh (from *Zea mays*)

5

3800 mg Magnesium stearate USP

(Optionally one can add 10000 gm of enteric coated
microspheres containing 500 gm of naloxone hydrochloride
10 prepared according to the procedure of Example 5 herein.

This composition is used to generate 400,000 tablets
weighing 1.05 gm each.

Alternatively, the mixture may be filled into hard
15 gelatin capsules in place of tabletting.

A starch paste is prepared by mixing 4000 gm of starch
with 8000 gm of deionized water. A separate blend is
prepared by mixing 2500 gm of starch, 16000gm of
20 methadone hydrochloride and 40,000 gm of anhydrous
lactose. The naloxone hydrochloride (800 gm) is
dissolved in 1500 gm of deionized water. The starch,
methadone hydrochloride, and anhydrous lactose. The wet
granulation is passed through a No 10 mesh screen, spread
25 on trays and dried for 18 hours at 120o F. The moisture
content of the dried granulation is between 2.0-3.5%. The
dried granulation is then consecutively passed through a
No. 12 mesh screen and a No. 30 mesh screen.

30 To the dried granulation there are added 950 gm of
xanthan gum (Keltrol F), 3700 gm of locust bean gum, 700
gm of monobasic calcium phosphate, 700 gm of dibasic
calcium phosphate, 24,800 gm of microcrystalline
cellulose (Avicel), and 500 gm of F .D. and C. yellow
35 lake no. 5 and the mixture is blended for 15 minutes.
Propylene glycol alginate (Kelcoloid HVF -10,000 gm),
which has been compacted and granulated to produce 25-30
mesh granules 950 gm of magnesium stearate are added the
mixture is blended for five minutes. Optionally, the
40 mixture may then be admixed with 40,000 gm of enteric
coated microspheres containing 2000 gm of enteric coated
naloxone hydrochloride.

- 5 This mixture makes 400,000 tablets each weighing 1.05 gm
and containing 40 mg of methadone hydrochloride and 2 mg
of naloxone hydrochloride, in addition to 5 mg of enteric
coated naloxone hydrochloride. Alternatively to
10 tabletting the mixture may be filled into hard gelatin
capsules.

Example 3

methadone-naloxone (5 + 0.25) For Analgesia

15 Components

	Methadone hydrochloride	500 gm
	Naloxone hydrochloride	25 gm
	starch U.S.P. (for paste)	4,000 gm
	starch U.S.P. (for granulation)	10,000 gm
20	lactose U.S.P. anhydrous	160,100 gm
	kehrol F	3,700 gm
	locust bean gum	14,800 gm
	monobasic calcium phosphate, anhydrous	2,800 gm
	di-calcium phosphate N.F. anhydrous	2,800 gm
25	microcrystalline cellulose	99,200 gm
	Kelcoloid HVF	40,000 gm
	F D and C Yellow No. 5 lake	2,000 gm
	Zein F-4000	20,000 gm
	Magnesium stearate USP	3,800 gm

- 30 The preparation of this dosage form is exactly as
described for Example 1, except for the substitution of
methadone hydrochloride for oxycodone hydrochloride.

Example 4

- 35 (Paregoric-Naloxone) Tablets or
Capsules

Components

Opium powder	400 gm
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5	Naloxone hydrochloride	20 gm
	Starch U.S.P. (for paste)	1000 gm
	Starch U.S.P. (for granulation)	2500 gm
	Lactose (anhydrous)	40000 gm
	Keltrol F	950 gm
10	Locust bean gum	3700 gm
	Monobasic calcium phosphate	700 gm
	Dibasic calcium phosphate	700 gm
	Microcrystalline cellulose	24800 gm
	Kelcoloid HVF 18	10000 gm
15	F .D. and C. yellow lake No.5	500 gm
	Zein F-4000	5000 gm
	Magnesium stearate U.S.P.	950 gm
	Preparation is exactly as in example 1 substituting opium powder for oxycodone hydrochloride. This formula makes	
20	100,000 tablets, or optionally, hard gelatin capsules wherein the dose of opium powder is 4mg and the dose of naloxone is 0.2mg and from one to two tablets may be taken every 4 hours up to six times a day for simple diarrhea.	

25

EXAMPLE 5

Naloxone hydrochloride enteric coated
non-pareil pellets

30

Naloxone hydrochloride antidiarrheal pellets, for
inclusion into analgetic-naloxone
tablets (see examples I-IV), having the following
35 formulation were prepared.

	Naloxone hydrochloride	0.134 kg
	Sugar spheres (non-pareil)	5.68 kg
	Ethylcellulose, NF (Ethocel)	1.40 kg
40	Polysorbate 80 NF	0.12 kg
	Isopropyl alcohol USP*	32.57 kg

5 (*Evaporated during processing)

Total weight 7.226 kg containing about 135,000
nonpareils, each containing about 1 mg of naloxone
hydrochloride. Thus each final dosage forms should have
10 about 3 to 10 beads.

Add the ethylcellulose to the isopropyl alcohol in a
stainless steel tank. The naloxone hydrochloride
(micronized) is added to the ethylcellulose solution with
15 continuous agitation for at least 10 minutes with a
homogenizer under conditions that avoid the formation of
lumps or the introduction of air which causes foaming.
The polysorbate 80 is then added while mixing in a
homogenizer. The coating solution is sprayed onto the
20 sugar spheres in a fluidized bed coater under the
following conditions: product temperature 20-35° -C.;
atomization pressure 2-4 bars; air volume 700-1800 m3/L.
and a pump rate of 300-1500 mg/min. After spraying, the
pellets are dried in the fluidized bed coater for
25 approximately 10 minutes and then cooled and collected
using a particle size separator.

The naloxone coated pellets are then coated with the
enteric polymer to form enteric polymer membrane coated
30 slow release pellets as follows:

Naloxone coated pellets	3.29 kg
Methacrylic acid copolymer (Eudragit S100)	0.167 kg
35 Acetyl tributyl citrate	0.027 kg
Talc USP	0.056 kg
Isopropyl alcohol USP	3.70 kg
Purified water USP	0.10 kg

40 The total weight of the coating solution plus
pellets is 7.5 kg.

5 The acetyl tributyl citrate (plasticizer) is dissolved
in the isopropyl alcohol in a stainless steel tank while
homogenizing. The Eudragit S100 (poly methacrylate, (2-
dimethyl aminoethyl) methacrylate, methyl methacrylate)
1:2:1) is added to the above mixture until it completely
10 dissolves. Purified water is added to the polymer mixture
to provide a clear solution. Then the talc is dispersed
into the solution while mixing until a uniform
coatingsuspension is formed. The suspension is
continually stirred throughout the coating process to
15 prevent sedimentation of the talc.
The following conditions are used during the spray
coating: product temperature; first hour 35-40° C.,
thereafter 32-35°C; atomization pressure; 3-4 bar; pump
rate; first hour 300-600 g/min; then 600-1500 gm/min.
20 After all coating suspension is consumed, dry the pellets
in the fluidized bed for 5 minutes. Then cool the pellets
until the temperature drops to 25-30° C. and discharge the
pellets while dusting with talc. The pellets are then
dried in an oven at 60 degrees C for at least 40 hours.

25

EXAMPLE 6

COATED NALOXONE PELLETS

30 Preparation of naloxone pellets by the method of
extrusion-spheronization

A mix of naloxone hydrochloride (60%) and Avicel PH101
(FMC, Belgium) (40%) is wetted with additional water
35 (52.5%) in a planetary mixer. Wet powder masses are
loaded into an Alexanderwerk GA65 gravity feed extruder.
The extrudate is spheronized in a Caleva 12 cm
spheronizer fitted with a cross-hatch friction plate for
10 min. at 1250 rpm speed. After drying of the
40 spheronized product at 45° C., sieving analysis is
performed using a nest of standard sieves, and the
desirable range of pellets was selected between 0.85 and
1.16 mm.

5

Coat application by pan technology

A load of pellets (approximately 1 mm in diameter) is placed into a coating pan pre-roughened with
10 polyvinylpyrrolidone/talc. A 20% w/v dispersion of guar-Eudragit S100 (1:4) in isopropanol-water (1:1) (350gms. of Eudragit S100; 1400gms of isopropanol; 100gms talc/ 3000gms of pellets (spheres)) is delivered to the cores and a stream of drying air at 60° C. was applied to the
15 surface of the cores. Coat application is continued until a 40% coating weight gain was achieved. The microcapsules are cured at 450 C. for 12 hours in a forced air circulation oven, after which they are stored at 20° C. for 7-14 days prior to use. The coated sphere contain
20 about 0.5 gm naloxone and thus the final dosage form will use about 6-20 beads.

EXAMPLE 7

(sustained release oxycodone plus naloxone
25 for administration every 12 hours; the particular dose is dependent on the relative severity of the pain)

This analgetic preparation may be made in five sizes as follows:

30

Size A: 10 mg of oxycodone hydrochloride plus 0.5 mg of naloxone hydrochloride

35

Size B 20 mg of oxycodone hydrochloride plus 1.0 mg of naloxone hydrochloride

Size C 40 mg of oxycodone hydrochloride plus 2.0 mg of naloxone hydrochloride

40

Size D 80 mg of oxycodone hydrochloride plus 4.0 mg of naloxone hydrochloride

- 5 Size E 160 mg of oxycodone hydrochloride plus 8.0 mg of
naloxone hydrochloride

In the sustained release mixture for each size of tablet
or capsule one-third of the above content are in an
10 immediate release form, one-third of the above content
are compounded with 1/20 Eudragit L 100 for release in
four hours in the jejunum, and one-third of the above
content are compounded with 1/20 Eudragit S 100 for
release in eight hours in the ileum. The preparation and
15 coating of the sustained release pellets is carried out
as described in Example 6.

Components:

20	Oxycodone hydrochloride	For	Size A	
	1000 gm			
		Size B	2000 gm	
		Size C	4000 gm	
		Size D	8000 gm	
25		Size E	16000 gm	
	Naloxone hydrochloride	For	Size A	50 gm
30		Size B	100 gm	
		Size C	200 gm	
		Size D	400 gm	
		Size E	800 gm	
35	Starch U.S.P. (for paste)		1000 gm	
	Starch U.S.P. (for granulation)		2500 gm	
	Lactose (anhydrous)		40000 gm	
	Keltrol F (xanthan gum from Xanthamonas)		950 gm	
	Locust bean gum (from Serotonia siliqua		3700 gm	
40	Monobasic calcium phosphate		700 gm	
	Dibasic calcium phosphate		700 gm	
	Microcrystalline cellulose (Avicel)		24800 gm	
	Kelcoloid HVF 18		10000 gm	

5 F .D. and C. yellow lake No.5 500 gm
Zein F 4000 20-30 mesh 5000 gm
Magnesium Stearate U.S.P. 950 gm

10 Example 8 (Sustained Release
Oxycodone plus Naloxone)

Procedure carried out as in example 7, with the addition
of 5 mg of naloxone hydrochloride per tablet to limit
constipation.

15